

clinical practice guidelines

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Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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incidence and epidemiology

The yearly incidence of acute myeloblastic leukaemia (AML) in European adults is five to eight cases per 100 000 individuals with a steep increase in the population aged over 70 years where the incidence reaches 15–25/100 000 per annum. The yearly mortality figure in AML is four to six cases per 100 000.

diagnosis and pathology/molecular biology

The diagnosis of AML requires the examination of peripheral blood and bone marrow specimens. The work-up of these specimens should include morphology, cytochemistry, immunophenotyping, cytogenetics and molecular genetics [chiefly polymerase chain reaction (PCR) and fluorescence *in situ* hybridisation (FISH) techniques]. See Table 1.

Whilst historically sorted by the largely descriptive French-American-British (FAB) criteria [1], AML are now classified according to the World Health Organisation (WHO) classification from 2001, revised in 2008 [2–4]. The WHO classification incorporates, in addition to morphological criteria, cytogenetic data, molecular genetics, immunophenotype data and clinical information into a diagnostic algorithm to delineate clinically significant disease entities. In the WHO classification the term ‘myeloid’ includes all cells belonging to the granulocytic, monocyte/macrophage, erythroid, megakaryocytic and mast cell lineage. The percentage of blast cells in the bone marrow is a practical tool for categorising myeloid neoplasms into AML or myelodysplastic syndromes (MDS), respectively, where myeloid neoplasms with more than 20% blasts in the peripheral blood or bone marrow are considered AML, either *de novo*, or having evolved from a pre-existing MDS. Blasts are defined using the criteria recently proposed by the International Working Group on Morphology of MDS.

risk assessment and prognostic factors

Patient age, initial leukocyte counts and co-morbidity are important risk factors. AML having evolved from previously documented MDS generally have an adverse prognosis. Molecular and genetic risk stratification are the key principles to guide the therapy of AML, and prognosis is chiefly governed by AML subtypes or entities defined through their karyotype or specific molecular features [I, A] [5–11].

karyotype/cytogenetics

The most favourable types of AML are acute promyelocytic leukaemia (APL) with the chromosomal translocation t(15;17) (q22;q12), and AML with the t(8;21)(q22;q22), inv(16) (p13.1q22) or t(16;16)(p13.1;q22) (mostly myelomonocytic leukaemia with preponderance of eosinophil granulocytes in the bone marrow), termed core binding factor acute myeloblastic leukaemia (CBF-AML). Patients with normal karyotype AML are in an intermediate risk group, and AML with complex karyotype abnormalities and/or chromosomal monosomies fare poorly [I, A]. See Table 2.

molecular genetics

Good-risk translocations in AML defined above are all amenable to detection with molecular techniques (PCR or FISH) which may be faster than classical cytogenetics, and are therefore recommended. In cytogenetically normal AML, somatic mutations of the genes FLT3 (a receptor tyrosine kinase), NPM1 (nucleophosmin) or CEBPα (a transcription factor) have been identified as important prognostic factors. NPM1 and bi-allelic CEBPα mutations are favourable when present as single molecular aberrations. FLT3 alterations present as a single molecular abnormality or with a high allelic ratio predict for a high (and early) relapse rate [10–13]. Patients with abnormalities of the chromosomal region 11q23 representing the mixed lineage leukaemia (MLL) gene fare poorly [I, A]. The list of genes with diagnostic and prognostic value will certainly increase, for example to include gene mutations in the isocitrate dehydrogenase (IDH) genes or in the *tet* oncogene family member 2 (TET2) genes; in addition, the genes for DNA (cytosine-5)-methyltransferase 3 α (DNMT3A), Runt-related

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Table 1. Diagnostic work-up in AML

- Bone marrow aspirate and biopsy as well as peripheral blood films
- Immunophenotyping of peripheral blood and bone marrow aspirates
- Cytogenetics and molecular genetics (PCR and FISH techniques)
- Routine chemistry including liver and kidney parameters
- Coagulation profile
- Blood group and HLA typing of patient and family members
- Radiology to include dental survey as well as CT scan of chest and abdomen (or chest X-ray and abdominal ultrasound)
- Sperm preservation in men (according to patient preference)
- Serum pregnancy test in female patients

Table 2. AML risk factors

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|--------------|--|
| Favourable | APL with t(15;17) |
| | CBF-AML with t(8;21) or inv 16 |
| | Biallelic CEBP α mutation with normal cytogenetics |
| | Normal karyotype with NPM mutation and no FLT3 ITD |
| Intermediate | AML with normal cytogenetics and no adverse molecular features |
| | FLT3 ITD with normal karyotype |
| Adverse | Complex karyotype abnormalities (>3) |
| | Monosomal karyotype |

transcription factor 1 (RUNX1) and additional sex combs-like 1 (ASXL1) may be listed. However, these 'newer' markers do not have an established use in routine practice at present. Gene expression profiles assessed by microarray technology have been reported to split AML into defined sub-/categories, but these techniques are not yet ready for widespread routine use. The same applies to the techniques of next-generation sequencing of AML cases.

co-morbidity and other host factors

Patients aged ≥ 60 –65 years are more susceptible to treatment complications (particularly severe infections) than younger patients, which contributes to higher risk of an unfavourable outcome. Pre-existing medical conditions such as diabetes, coronary heart disease, or chronic pulmonary obstructive disease must also be recognised as contributing to poor risk. It is recommended to assess cardiac risk factors at diagnosis, in addition to clinical examination and cardiac echocardiography.

At diagnosis, patients should be investigated for the presence of active infection, particularly those planned for intensive treatment. Careful clinical and haematological assessment is required to identify such patients where the start of chemotherapy could or should be delayed, until active infection has been treated. In addition to clinical examination, additional techniques recommended are computed tomography (CT) scans of the chest and the abdomen, and radiological imaging of teeth and jaws to identify infectious foci such as dental root granulomas and caries. In addition to haematological and chemistry laboratory tests, a coagulation status must be obtained to detect leukaemia-related coagulopathy, particularly in APL; such tests must be carried out before the insertion of central intravenous lines.

other pre-treatment investigations

Patients potentially suitable for allogeneic stem cell transplantation (alloSCT) should be human leukocyte antigen (HLA) typed at diagnosis, as should their available first- and second-degree family members. In high-risk disease (e.g. poor-risk karyotype), early matched unrelated donor (MUD) allogeneic transplantation must be considered, and therefore, a donor search should be carried out as early as possible [I, A].

treatment

Whenever possible, AML treatment should be offered in clinical trials, and given only in experienced centres offering an adequate multidisciplinary infrastructure as well as a suitably high case load [14, 15]. Treatment should be planned with curative intent whenever possible. Intensive chemotherapy of AML is divided into an induction phase, consolidation and (rarely) maintenance. Potential candidates for alloSCT (scheduled for the consolidation phase) must be identified early at diagnosis or during induction chemotherapy [I, A]. Treatment of APL differs in several important aspects from therapy of all other AML types and is, therefore, discussed in a separate section.

intensive treatment of non-APL AML

All patients undergoing intensive chemotherapy need a central intravenous line inserted, if necessary, under platelet transfusion. Induction chemotherapy should only be started (if possible) when all material needed for diagnostic testing has been satisfactorily sampled. Patients with excessive leukocytosis at presentation and with clinical signs of leukostasis may require emergency leukapheresis coordinated with the start of chemotherapy. These patients are at particular risk of a tumour lysis syndrome under induction chemotherapy and need appropriate monitoring. In these cases a single injection of rasburicase may be considered to prevent hyperuricaemia and hence renal failure, but data are insufficient to support a firm recommendation in this respect. In most patients with AML, the start of treatment can safely be postponed for several days until all diagnostic material has been collected and the results of analyses such as molecular typing are available.

Induction chemotherapy should include an anthracycline and cytarabine with the particularly well-known and time-honoured '3 + 7' regimen [I, A]. Data on dose escalation of daunorubicin to improve AML outcome look promising, but longer follow-up is required to support a firm recommendation [II, C]. Haematopoietic growth factors are an optional adjunct to intensive induction chemotherapy; however, evidence on their role in reducing the incidence and/or the severity of infectious complications during bone marrow aplasia, and evidence on their putative benefit conferred through priming of leukaemic cells to increase sensitivity to cytostatic agents, is not convincing [II, C] [13, 15–20].

Consolidation therapy in AML is warranted once patients have reached clinical and haematological remission [I, A]. There is no consensus on a single 'best' post-remission treatment

schedule. In good-risk AML patients in first remission, who have a relapse risk of 35% or less, alloSCT is not justified because its toxic effect and/or its risk of transplantation-related mortality exceed the benefit. Also, these patients may receive salvage therapy including alloSCT in second remission. Good-risk AML patients (including NPM-mutated AML with absence of internal tandem duplications of FLT3 (FLT3-ITD), CBF AML, and bi-allelic mutant CEBP α AML) as well as patients who are unsuitable for alloSCT for other reasons should receive at least one cycle of intensive consolidation chemotherapy preferably incorporating intermediate or high-dose cytarabine [I, A]. Patients with AML in intermediate- and poor-risk groups with an HLA-identical sibling may be candidates for alloSCT, provided their age and performance status allow for such treatment [21–32]. Newer data suggest that alloSCT may no longer be mandatory in intermediate risk patients, but these data need to be confirmed [III, C] [15]. Patients in these risk groups without a family donor may qualify for alloSCT with an HLA-matched unrelated donor identified through an international donor registry. In fact, peripheral stem cells harvested from unrelated HLA-matched donors have become the most frequently used source of stem cells. If a killer-immunoglobulin-like receptor (KIR) mismatch is present, haploidentical transplants may be considered. Conditioning regimens for alloSCT with dose-reduced chemotherapy intensity (RIC) may be used for patients in the upper age range (particularly those >50 years of age), but there is some evidence that RIC may also be used in adults at a younger age [II, B]. Infectious disease complications contracted during induction should be under suitable control before an alloSCT is enacted. The role of high-dose chemotherapy with autologous stem cell re-transfusion in AML is still controversial. Recent data suggest that it may be a good option (and thus an alternative to alloSCT) in patients in an intermediate risk group [19]. Whilst it may prolong time to relapse or remission duration, its potential to prolong overall survival is uncertain [I, C] [23, 25–27].

non-intensive treatment of AML

Patients with significant co-morbidity and the elderly are often not eligible for intensive treatment. They should receive best supportive care (BSC) or palliative systemic treatment, which may incorporate either low-dose cytarabine or a demethylating agent such as decitabine or azacitidine [II, B]. Excessive leukocytosis due to spilling of malignant blasts into the periphery may be reduced with cytoreductive agents such as hydroxyurea or low-dose cytarabine, which, however, also lower normal blood cell counts such as red cells, neutrophils or platelets. Treatment of infections due to neutropenia and transfusions to cover anaemia or thrombocytopenia are important additional measures. Erythropoietin is of questionable value in patients with anaemia due to extensive infiltration of the marrow with leukaemia. In severely neutropenic patients haematopoietic growth factors may be tried when neutropenic fever or infections are a problem; however, there is no evidence to support their continuous use [II, D] [13, 17, 23, 32–35].

therapy of refractory or relapsed AML

Resistance to therapy (refractory or relapsed AML) is the major cause of treatment failure, rather than mortality due to infections and other treatment-related complications. Patients failing to respond to one or two cycles of induction treatment are considered refractory and are at very high risk of ultimate treatment failure. Carefully selected patients with an HLA-matched donor may be offered alloSCT, albeit with limited chances of success and at the cost of considerable morbidity from this procedure [II, B]. For patients unsuited to this approach, BSC or palliative systemic treatment is often a reasonable option with, at least, limited toxic effect. The prognosis of such patients is often dismal regardless of treatment attempts.

Patients presenting with relapse after a first remission may be offered intensive re-induction, for which chances of success are better after longer duration of first remission. Patients in second or subsequent remission may still qualify for alloSCT with a family or unrelated HLA-matched donor, or with cord blood-derived stem cells.

treatment of APL

Suspicion of or established diagnosis of APL must trigger a distinctive therapy programme [36–39]. If in doubt and/or if APL is a diagnostic possibility at presentation, oral all-trans retinoic acid (ATRA) should immediately be started, and only discontinued when APL has been specifically excluded in the diagnostic work-up of newly diagnosed AML [I, A]. Risk assessment of APL is chiefly based on white blood cell (WBC) count at presentation, where patients with a WBC count >10 000/mm³ fare worse. APL induction chemotherapy consists of ATRA as a differentiating agent and an anthracycline given simultaneously, but the role of cytarabine in the treatment of APL is controversial. The use of arsenic trioxide (ATO) in first-line APL therapy is promising, but long-term results are not yet available. However, the results of ATRA-ATO therapy without chemotherapy look promising, particularly in good risk APL [II, C] [40]. The need for daily i.v. application of ATO over a prolonged period of time, electrolyte as well as cardiac problems (including potentially fatal *torsade-de-pointe* ventricular arrhythmias) and case reports on secondary cancers after ATO must all be considered. If the results of ASO-ATRA induction (without chemotherapy) hold true over time, this regime might well become a new future standard, at least in low- to intermediate-risk APL [II, C] [40]. Primary resistance of APL is virtually unheard of and must infer a revision of the initial diagnosis. APL patients must be followed very closely for the development of leukaemia-associated coagulopathy and haemorrhage at presentation and/or under induction. Their platelet counts should be kept at a minimum of 30–50 G/l. Fibrinogen should be kept in the normal range (100–150 mg/dl) throughout induction, whenever possible until signs of coagulopathy subside. The use of heparin is controversial and is not recommended as a routine procedure.

The optimal strategy of consolidation in APL is less clear, but there is consensus on giving two to three anthracycline-containing chemotherapy cycles [II, B]. A high proportion of patients reach molecular remission after this treatment series,

where the t(15;17) is no longer PCR-detectable. The small fraction of patients with persistent molecular disease (i.e. with the molecular equivalent of the t(15;17) still detectable with sensitive quantitative PCR assays) may need maintenance therapy including non-marrow ablative long-term chemotherapy and ATRA. There is no role for alloSCT in patients with APL in first remission.

In relapsed APL, ATO can induce remissions, even in patients having turned refractory to ATRA [II, B]. It should be given until remission is documented. Patients at particularly high risk for later additional APL relapses may be candidates for alloSCT or for high-dose chemotherapy consolidation with re-transfusion of autologous stem cells.

personalised medicine

The impact of molecular AML typing has been demonstrated extensively for diagnostic purposes (to define AML entities or subtypes) and for AML risk assessment (see above section) [5, 6, 9, 12, 13]. However, AML molecular genotyping still has relatively little practical use in predicting specific drug treatment. APL is the only type of AML for which a targeted agent (ATRA) has become mandatory in routine practice [I, A]. For all other AML entities, targeted agents are either not available, e.g. for core-binding factor leukaemias, or are still experimental, e.g. the treatment of FLT-3-positive AML with the tyrosine kinase inhibitors sorafenib or midostaurin [41]. A monoclonal antibody targeting the CD33 antigen often present on AML blasts has shown discordant results in clinical trials; hence, no firm recommendation for its routine application can be given [II, D] [42].

response evaluation and follow-up

Response of AML to treatment is monitored clinically, with serial peripheral blood counts and repeat bone marrow examinations. During intensive chemotherapy, bone marrow should be examined in the aplastic phase to monitor blast clearance, persistence or early relapse. The usually accepted criteria of response in AML are blast clearance in the bone marrow to <5% of all nucleated cells, morphologically normal haematopoiesis and return of peripheral blood cell counts to normal levels. Clearance of infections contracted during therapy-induced aplasia should also be documented.

Patients having concluded treatment should be followed clinically and with repeated haematological examinations. Serial bone marrow examinations of patients in remission are of uncertain value, and cannot therefore be generally recommended. Although sensitive PCR methods as well as immunophenotyping are available, permitting molecular follow-up and detection of minimal residual disease in patients with suitable markers (mostly specific chromosomal translocations, or typical antigen expression profiles, respectively), the early detection of molecular relapse in the absence of morphological evidence for recurrent AML is of uncertain therapeutic consequence. Specifically, evidence that early re-induction treatment of such patients still in haematological remission would be of any benefit is lacking.

note

A summary of recommendations is provided in Table 3. Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Table 3. Summary of recommendations

- Diagnostic work-up of AML must include morphology of peripheral blood and bone marrow, cytogenetics and molecular genetics assessed before start of therapy
- HLA-typing of patient and family members to plan for allogeneic stem cell transplantation where indicated
- AML should only be treated in specialised and experienced centres offering a multidisciplinary approach, and the possibility of clinical trials
- AML therapy with curative intent includes induction chemotherapy (incorporating an anthracycline and cytarabine), consolidation which in intermediate to high-risk patients may incorporate allogeneic stem cell transplantation
- APL needs a specific therapy approach. ATRA must be started whenever in a case of leukaemia the differential diagnosis of APL is considered, and combined with anthracycline-based chemotherapy once the diagnosis of APL is confirmed

Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

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|--------------------------|--|
| Levels of evidence | |
| I | Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity |
| II | Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies or case-control studies |
| V | Studies without control group, case reports, experts opinions |
| Grades of recommendation | |
| A | Strong evidence for efficacy with a substantial clinical benefit, strongly recommended |
| B | Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended |
| C | Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional |
| D | Moderate evidence against efficacy or for adverse outcome, generally not recommended |
| E | Strong evidence against efficacy or for adverse outcome, never recommended |

^aDykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139-144. By permission of the Infectious Diseases Society of America.

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conflict of interest

Prof. Buske has reported consultancy/honoraria from Celgene, Pfizer and Roche. Prof. Fey has reported no potential conflicts of interest.

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